Remarks/Arguments

I. Claim Amendments

Amendments to claims are reflected in the listing of claims from page 4 to 8 of this communication. The term "a mammalian *in vitro* mRNA decapping system" is supported by page 14, lines 14 and 19. The term "substantially free of polysomes" is supported by page 15, lines 6-9.

In the newly added claims 22, 23, 25, 27, 29, 33 and 35, Applicants present means-plus-function limitations. Means-plus-function limitations are proper claim formats under 35 U.S.C. 112, sixth paragraph, and are construed to be limited to the corresponding structures or materials disclosed in the specification. In re Donaldson Co., 29 USPQ.2d 1845 (Fed. Cir. 1984).

Means for decapping a cap-labeled mRNA substrate is supported by page 31, lines 23-24. Means for stimulating decapping is supported by page 33, lines 27-29. Means for reducing decapping is supported by page 35, lines 15-16. Means for sequestering proteins that bind to poly(A) is supported by page 20, lines 9-10 of Application No. 09/320,609, which is incorporated by reference in its entirety (p. 2, ll. 21-23).

II. Priority

The Office Action objects to granting Applicants' claim for priority to U.S. provisional application 60/223,682 under 35 U.S.C. 119(e), asserting that the "application is not properly referenced in the declaration".

The first paragraph of the specification states that this "application claims priority under 35 U.S.C. 119(e) from U.S. Serial No. 60/233,682, filed September 19, 2000, which is incorporated herein by reference in its entirety". Applicants have submitted a new declaration attached hereto, which claims the benefit of the U.S. Provisional Application No. 60/233,682, filed September 19, 2000. Applicants believe that the Provisional Application No. 60/233,682 is now properly referenced in the new declaration. Accordingly, Applicants respectfully request that Applicants' claim for priority to the Provisional Application No. 60/233, 682 be granted.

III. Oath/Declaration

The Office Action objects to the declaration filed December 18, 2001 as being defective. Applicants submit a new declaration attached hereto. Applicants believe that the new declaration corrects the deficiencies that are objected to in the Office Action. Accordingly, Applicants respectfully request that the objection be withdrawn.

IV. Claim Objections

Claim 3 is objected to due to a grammatical error. Applicants have corrected the error and therefore respectfully request that the objection be reconsidered and withdrawn.

Claim 4 is objected to. Applicants have cancelled claim 4 and therefore made the objection moot.

V. Claim r jections under 35 U.S.C. 112 for lack of enablement.

Claims 1-13 and 17-21 are rejected under 35 U.S.C. 112, first paragraph. The Office Action acknowledges that the specification is enabling for an S100 Hela Cell extract. However, the Office Action asserts that the specification does not provide reasonable enablement for all mammalian cell extracts. To the extent the rejection can be applied to the amended claims, Applicants respectfully traverse.

(i) Applicants heed the rulings of In re Wands

It is well established that undue experimentation would not be required to practice the invention when the "disclosure provides considerable direction and guidance on how to practice their invention and presents working examples" and "all of the methods needed to practice the invention were well known". In re Wands, 858 F.2d 731, 740 (1988). Furthermore, "it seems unlikely that undue experimentation would be defined in terms of the number of experiments." Id. A considerable amount of experimentation is permissible, if it is merely routine. 858 F.2d at 737.

Applicants track precisely the rulings of Wands. Applicants provide considerable direction and guidance on how to practice the claimed invention with respect to the mammalian cell extracts substantially free of polysomes. In preparing the extract, Applicants teaches that cells can be grown, harvested, lysed and centrifuged for 100,000 x g for I hour (p. 19, ll. 12-14). Additionally, the extract which is as free of polysomes as possible can be prepared from lysed mammalian cells by any method known in the art (p. 15, ll. 6-9).

To determine whether a mammalian cell extract contain a decapping activity, Applicants use a Hela cell extract as an example to describe the procedures (See, p. 6, ll. 17-29, p. 28, l. 10 to p. 32, l. 1). Briefly, Applicants teach that a cap-labeled mRNA is incubated with an extract (the Hela cell extract as a example), a methylated cap analog is added into the mixture, and a decapping product, e.g., ^{7me}GDP, is measured using thin layer chromatography (TLC) on PEI cellulose sheets. The accumulation of ^{7me}GDP indicates that the extract contains a decapping activity (p. 31, ll. 22-24). Given that ^{7me}GDP is observed in TLC upon the addition of a methylated cap analog in the Hela cell extract, Applicants conclude that the Hela cytoplasmic extract contains a decapping activity (Fig. 1B, p. 31, ll. 28-29). By the same token, a skilled artisan can follow Applicants' teaching and determine whether a mammalian cell extract substantially free of polysomes contains a decapping activity by observing the accumulation of the decapping product ^{7me}GDP in the presence of the extract, a cap analog and a cap-labeled mRNA substrate. It is noted that undue experimentation would unlikely be defined in terms of the number of experiments. Wands, 858 F.2d at 740.

Applicants further note that all the method used in the specification are routine. In particular, the methods of making mammalian cell extract substantially free of polysomes, synthesizing mRNA, labeling the cap, and measuring the accumulation of ^{7me}GDP using TLC are all well known in the art and routinely practiced.

Given that Applicants provide considerable direction and guidance in the specification, that Applicants present the Hela cell extract as a working example, and that all the methods needed to practice the claimed invention are routine, Applicants find no reason why it would require undue experimentation for one skilled in the art to make and/or use claimed mammalian cell extracts substantially free of polysomes.

(ii) Applicants weigh *Forman* factors.

The factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Forman, 230 U.S.P.Q. 546 (1986) (reiterated in In re Wands, 858 F.2d at 737). They include 1) the nature of the invention; 2) the scope/breath of the invention/; 3) the state of the art; 4) the number of working examples or guidance presented; 5) the level of skill in the art; 6) the predictability or unpredictability of the art.

The Nature of the Invention. The Office Action correctly points out that the primary aspect of invention is a mammalian cytoplasmic extract with the intended use of biochemically measuring the decapping of mRNA species. Applicants appreciate the Office Action's acknowledgement that the invention is novel in that no one had previously been able to detect this activity in mammalian cells (The Office Action, p. 4).

The State of the Art. The Office Action asserts that the state of art is underdeveloped since there is currently no direct biochemical evidence for decapping in mammalian cells. Applicants respectfully traverse. The fact that there

was no direct biochemical evidence for decapping in mammalian cells does not suggest that the state of the decapping art is underdeveloped. At most, this merely means that decapping in mammalian cells was unrecognized and unappreciated prior to Applicants' invention (p. 13, ll. 28). This leads to one aspect of Applicants' invention that the decapping activity in mammalian cells is masked in *in vitro* assay[s] (p. 31, ll. 10-11) and the addition of methylated cap analogs activates the decapping activity (p.17, ll. 2-5). However, the art regarding the measurement of decapping mRNA has long been developed, particularly in yeast. For review, see Tucker & Parker, Mechanism and Control of mRNA Decapping in Saccharomyces cerevisiae, *Annu. Rev. Biochem.* 69:571-95 (2000). Accordingly, it appears that the state of the art has well been developed.

The Number of Working Examples or Guidance Presented. The Office Action concedes that the specification provides guidance and working examples regarding the use of the Hela cell extract. However, the Office Action asserts that the specification does not provide guidance to the use of other mammalian cells. As discussed in Section V(i) of this paper, Applicants point out that the specification provides considerable guidance that allows a skilled artisan to make and/or use any mammalian cell extract containing the decapping activity. Accordingly, the specification provides working examples and guidance for the claimed mammalian cell extract.

The Level of Skill in the Art. The Office Action asserts that the level of skill in the art is under-developed since no one has previously been able to measure mRNA

decapping in mammalian extracts. The fact that no one has been able to measure mRNA decapping in mammalian extracts does not suggest the level of skill in the art is underdeveloped. Simply, measuring mRNA decapping in mammalian extracts was unrecognized and unappreciated due to the masking of decapping activity. On the other hand, Applicants note that all the methods used to measure mRNA decapping activity are well known and routinely practiced in the art (See Section V(I) of this paper). Therefore, Applicants believe that the level of skill in the art is well developed.

Predictability or Unpredictability of the Art. The Office Action asserts that the art is highly unpredictable since no one had previously been able to identify mRNA decapping in mammalian cell extracts. Applicants note that the reason no one had previously been able to identify mRNA decapping in mammalian cells is that the decapping activity was unrecognized and unappreciated due to the masking of decapping activity in mammalian cell extracts. Because Applicants teach that the addition of methylated cap analogs would activate the decapping activity in mammalian cell extracts, a skilled artisan would readily appreciate the effect of Applicants' teaching in measuring the decapping activity in the mammalian cell extracts. In other words, one skilled in the art would readily anticipate the effect of a change within the subject matter to which the claimed invention pertains. M.P.E.P. 2164.03 Further in view of Applicants' discussion in Section V (i) of this paper, Applicants believe that there is predictability in the art.

In light of the foregoing, Applicants believe that the specification enables a skilled artisan to make and/or use the claimed invention commensurate with the scope of these claims without undue experimentation. Applicants respectfully request that the rejections be reconsidered and withdrawn.

VI. Claim rejections under 35 U.S.C. 112 for inadequate written description.

Claims 7, 8, and 21 are rejected under 35 U.S.C. 112 as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey one skilled in the relevant art that the inventors at the time of the application was filed had possession of the claimed invention. Applicants have cancelled claims 7, 8, and 21 and therefore made the rejection moot.

VII. Claim rejections under 35 U.S.C. 112, second paragraph.

Claim 4 and 8 are rejected under 35 U.S.C. 112, second paragraph. Applicants have cancelled claim 4 and 8 and thereby made the rejection moot.

Claim 13 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite. In particular, the term "pyrimidine rich element" is not defined. Applicants note that the term "pyrimidine rich element" is well known in the art. To illustrate, the pyrimidine rich element is known as a consensus sequence with a nucleotide sequence of (C/U)CCAN$_x$CCC(U/A)Py$_x$UC(C/U)CC. Holcik & Liebhaber, Four highly stable eukaryotic mRNAs assemble 3' untranslated region RNA-protein complexes sharing cis and trans components, *Proc. Natl. Acad. Sci. U. S. A.* 94: 2410-2414 (1997).

Claims 17-21 are rejected as being indefinite. The Office Action suggests that the claims be directed to a kit that measuring mRNA decapping *in vitro*. Applicants have taken the Office Action's suggestion and amended the claims which are now directed to "a kit for measuring mRNA decapping in vitro". Accordingly, Applicants respectfully request that the rejections be reconsidered and withdrawn,

VIII. Claim rejections under 35 U.S.C. 102(b)

(i) Rejections of claims 1, 2, 4-6, 9, 10, and 17-20 as being anticipated by Ohno *et al.*

Claims 1, 2, 4-6, 9, 10, and 17-20 are rejected under 35 U.S.C. 102 (b) as being anticipated by Ohno *et al.*, A nuclear cap binding protein from Hela cells, Nuc. Acids. Res. 18: 6989-6995 (1990). In particular, the Office Action asserts that Ohno *et al.* teach a cytoplasmic S100 Hela cell extract containing a capped mRNA and a methylated cap analog for competition experiments. The Office Action further asserts that in Ohno *et al.* a high-salt cytoplasmic extract is centrifuged at 100,000 x g, a capped mRNA is synthesized using [α-^{32}P]GTP as a label, and a cap analog is ^{7me}GTP.

To the extent that the rejections can be applied to amended claims, Applicants respectfully traverse.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628 (Fed. Cir. 1987).

Applicant note that while Ohno *et al.* teach a mixture consisting of a Hela cell nuclear extract, a capped RNA and a ^{7me}GTP (See Lane 5 in Fig. 2), Ohno *et al.* do not teach a mixture consisting of a Hela cell cytoplasmic S100 fraction, a capped RNA and a ^{7me}GTP (See Lanes 6 and 7 in Fig. 2).

Applicants further note that Ohno *et al.* merely teach that a "capped RNA probe (58 nucleotide long including the block guanosine, 2-10X10^6 cpm/ug) was synthesized by ^{m7}GpppG-primed transcription of the plasmid pS64 linearized with EcoRI using SP6 RNA polymerase in the presence of [α-^{32}P] GTP." As a result, the cap, ^{m7}Gppp, in Ohno's RNA was not labeled although the remaining G residues of the RNA was labeled. In other words, Ohno *et al.* merely teach a labeled RNA with an unlabeled cap. In contrast, one of the elements of the claimed invention is directed to a cap-labeled mRNA substrate. It follows that Ohno *et al.* fail to teach or suggest each and every element of the claimed invention.

In light of the foregoing, claims 1, 2, 4-6, 9, 10, and 17-20 are not anticipated by Ohno *et al.* Accordingly, Applicants respectfully request that the rejections be reconsidered and withdrawn,

(ii) Rejections of claims 1, 4-6, 9, 10, and 17-20 as being anticipated by Hellmann *et al.*.

Claims 1, 4-6, 9, 10, and 17-20 are rejected under 35 U.S.C. 102 (b) as being anticipated by Hellmann *et al.*, A polypeptide which reverses cap analogue inhibition of cell-free protein synthesis, J. Biol. Chem. 257:4056-4062 (1982). In making the rejections, the Office Action asserts that Hellmann *et al.* teach a cytoplasmic

reticulocyte cell extract containing a capped mRNA and a methylated cap analog for competition experiments wherein ^{32}P is used to label the cap and the cap analog is ^{7me}GTP. To the extent that the rejections can be applied to the amended claims, Applicants respectfully traverse.

Applicants note that Hellmann *et al.* teach a cytoplasmic reticulocyte cell-free extract. It has been well known in the art that the reticulocyte cell-free extract contains all the macromolecular components required for translation of exogenous RNA, which include polysomes or ribosomes. See, Merrick, Translation of Exogenous mRNAs in Reticulocyte Lysates, *Meth. Enzymol.* 101: 606 – 615 (1983); Morley & Hershey, A Fractionated Reticulocyte Lysate Retains High Efficiency for Protein Synthesis, *Biochimie.* 72:259-264 (1990). On the other hand, the claimed mammalian cytoplasmic extract is substantially free of polysomes. It follows that Hellmann *et al.* fail to teach the claimed cytoplasmic extract.

Applicants further note that Hellmann *et al.* teach oligonucleotides in the form ^{7me}Gppp(Np)G (^{32}P)Cp (10-50,000 cpm/pmol). It appears that the cap of Hellmann's oligonucleotides is not labeled. Accordingly, Hellmann *et al.* fail to teach a cap-labeled mRNA.

In light of the foregoing, it appears that Hellmann *et al.* do not teach each and every element of the claimed invention. Accordingly, Applicants respectfully request that the rejections be withdrawn.

IX. Claim rejections under 35 U.S.C. 103(a)

Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ohno *et al.* in view of Robyt *et al.* (Biochemical Techniques: Theory and Practice, ISBN 0-534-07944-X (1987). In particular, the Office Action asserts that Robyt *et al.* teach dialysis and ordinary skilled artisan would have been motivated to combine both teachings to remove salt contamination from the extract prior to its storage. Applicants respectfully traverse.

To make a rejection under 35 U.S.C. 103(a), three basic criteria must be met. First, there must be some suggestion or motivation to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art references when combined must teach or suggest all the claim limitations. In re Vaeck, 947 F.2d 488 (Fed. Cir. 1991).

As discussed in Section VIII(i) of this paper, Ohno *et al.* do not teach a cap-labeled mRNA substrate. Accordingly, even if both references were to be combined, the combination does not suggest or teach all the claim limitations since the combination does render a cap-labeled mRNA.

In light of the foregoing, the rejection under 35 U.S.C. 103(a) is unsupported. Applicants respectfully request that the rejection be reconsidered and withdrawn.

References cited in this paper (Holcik & Liebhaber, Merrick, Morley & Hershey, Tucker & Parker) are enclosed herein and will be submitted under 37 CFR 1.97.

Applicants believe that the present amendment places the application in condition for allowance. A Notice of Allowance is, therefore, respectfully requested. If any additional issue needs to be addressed to expedite the prosecution of this application, please feel free to call the undersigned at (310) 788-3218.

Respectfully submitted,
Perkins Coie LLP

Date: 5/19/03

James J. Zhu
Registration No.52,396

Correspondence Address:

Perkins Coie LLP
Patent – LA
P.O. Box 1208
Seattle, WA 98111-1208
Phone: (310) 788-9900
Fax: (310) 788-3399